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REMARKS

The claims have been amended to further define the present invention and expedite prosecution. Specifically, claim 130 has been amended to recite that the cancer is of an epithelial origin and that the MMP has a molecular weight from 50 kDa to equal to or greater than 150 kDa. Support for these claim amendments can be found, for example, at page 3, line 36, page 10, lines 9 - 10, and page 3, lines 5 – 8. The new independent claims, claims 163 – 165, are directed to the use of a combination of MMPs and specific MMPs in the diagnosis of cancer. Support for the new claims can be found in the section noted above and throughout the specification. No new matter has been added by virtue of the amendments to the claims and the new claims.

As requested, the Specification has been updated regarding related applications and a new abstract is submitted herewith on a separate page.

With respect to the priority claim of the present application, this application is a continuation of Application No. 08/843,095, filed April 25, 1997, which is a continuation-in-part of Application No. 08/639,373 filed April 26, 1996. Parent Application No. 08/639,373 differs from continuation-in-part Application No. 08/843,095 by the absence of Example 9, Example 10, Table 14 and Table 15.

With regard to the February 23, 2000 IDS, copies of the references are enclosed herewith along with a copy of Form 1449.

With regard to the obviousness-type double patenting rejection, Applicants enclose a terminal disclosure executed by the undersigned attorney of record along with appropriate fee of $55.00.

Claims 130-162 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner takes the position that the specification, while possibly being enabling for specific enzymes and prostate cancer detected by specific MMP's, does not reasonably provide enablement for "a matrix metalloproteinase or "cancer".

Applicant's respectfully disagree and request that the rejection be withdrawn for the following reasons.

While great progress has been made in the treatment of cancer, it is universally accepted that cancer is easier to treat when detected early. There are several tests that are currently used for detection of cancer. These tests include looking at serum tumor markers such as PSA for prostate cancer, CEA for colorectal cancer and CA 125 for ovarian cancer. Other methods include, visualization of tumors using, for example, mammograms for breast cancer and colonoscopy for colon cancer. While these tests are accepted in the medical community, none is perfect.

For example, the tumor marker PSA has a 40% – 70% rate of false positives. Yet, PSA is the golden standard for prostate cancer detection.

The visualization methods, e.g., colonoscopy and mammography are highly invasive. Additionally, colonoscopy requires the doctor to visualize the tumor and then take action. Thus, results depend on the skill of the practitioner. Another drawback of these methods is that a tumor might have been growing for years before it is large enough to be detected. Even with these drawbacks, these methods are accepted in the medical community.

Turning to the Examiner's concerns raised in the office action, Applicants note that Table 3 sets forth the results of a small initial study. For the results of a larger study (117 specimens, 68 with cancer[1]), the Examiner is direct to Table 14, which shows an association between the presence of cancer and the presence of three MMPs (greater than or equal to 150 kDa, 92 kDa and 72 kDa). As set forth in Examples and illustrated in Table 14, the inventors have shown that the presence of MMPs in the urine is correlated with an increased likelihood of cancer of an

[1] As set forth at page 32, lines 18 – 24: These include 28 patients with **prostate** cancer, 10 with **renal** cancer, 10 with **bladder** cancer, 9 with **breast** cancer, and 11 with other cancer **(ovarian, lung, endometrial/cervical, testicular, lelomyosarcoma, adrenal pheochromocytoma, transitional cell carcinoma of kidney and lymphoma).** These samples from patients with organ-confined cancers were compared to those from 19 patients with metastatic cancer, 19 former cancer patients with no evidence of disease, and 22 normal volunteers.

the presence of MMPs in the urine is correlated with an increased likelihood of cancer of an epithelial origin. The frequencies of detection of one or more of these three urinary MMP species in each experimental group were: normal plus NED (control group), 8 of 49 (16%); NED (control group), 2 of 19 (11%); normal (control group), 6 of 30 (20%)[2]; cancer, 48 of 68 (71%); and metastatic cancer, 19 of 21 (90%). See, Moses et al., Exhibit H, page 1396, second column. The frequency of detection of at least one MMP species was significantly higher for both the cancer group and the metastatic cancer group, compared to each control group ($P < 0.001$). There were no significant differences between the two control groups ($P = 0.46$). The difference in detection of at least one MMP was higher for metastatic cancers than it was for organ-confined cancers, although this did not reach statistical significance ($P = 0.08$). The detection frequencies of one or more of these three MMPs were significantly higher for prostate (21 of 28, 75%), bladder (8 of 10, 80%), and breast (9 of 9, 100%) cancers as compared to the control groups (all $P < 0.001$). See, Table 14 and Moses et al., Exhibit H, page 1392, first column.

While the methods of the present invention are not perfect, no test is, the sensitivity and specificity are comparable to, or better than, those observed for currently medically accepted cancer markers PSA, CA 125 and CEA. However, the methods of the present invention have some important advantages. First, the methods of the present invention are **non-invasive.** Unlike currently used tumor markers, e.g., PSA, CA 125 and CEA, which require a blood sample, all that is required with the present invention is a urine sample. You can't get much more non-invasive than that.

Secondly, unlike the currently used tumor markers, that only detect one type of cancer, the methods of the present invention can screen for the presence of all cancers of epithelial origin. If the MMP screen is positive, the physician can then order more invasive and expensive tests in order to identify the particular cancer and pinpoint its location. Thus, the invention not only provides an increased likelihood of detecting cancer early, when it is most treatable, it saves

[2] The 20 % value is from Table 2 of Moses et al., Cancer Research 58, 1395 (1998), copy enclosed as Exhibit H. Table 14 of the present application sets this value as 23%. The data were recalculated for the Moses et al. publication resulting in slightly different values.

healthcare dollars by avoiding the initial use of expensive procedures for screening purposes. Additionally, the noninvasive nature of the present screen would encourage more people to be screened and, thus, increase the likelihood of detecting cancer earlier.

In addition, after the present invention, others have shown the correlation between urinary MMPs and **esophageal** and **ovarian** cancer (Hanemaaijer et al. Annals NY Acadamy of Sciences 1999 Jun 30,878:141-149, **Exhibit A**; Bazzett et al. Gynecologic Oncology 1999 March 72(3) 495-496, **Exhibit B**; Taylor et al. Proc. Of the American Association for Cancer Research Annual Meeting 2000 March, 41: 432, **Exhibit C**) as well as support those exemplified in the present application, such as lung, breast, renal and bladder cancer (Hanemaaijer et al. Annals NY Acadamy of Sciences 1999 Jun 30,878:141-149, **Exhibit A**; Sherief et. al. J. Urology 2003 169: 1530-1534, **Exhibit D**; Sherief et. al. J. Urology 2002 167(4) Supplement: 127-128, **Exhibit E;** Cornelis et. al. Clinical Cancer Research 2000, 6: 2333-2340, **Exhibit F**, El-Ahmady et. al. Anticancer Research 2002 Jan-Feb 22(IB): 504, **Exhibit G**).

In summary, it has been shown by the present inventors and others that MMPs are present in the urine of patients with at least 7 different types of cancers of epithelial origin, e.g., prostate, renal, bladder, breast, esophageal, ovarian and lung. Applicants respectfully submit that this showing is more than enough to satisfy the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 130-162 were rejected under 35 U.S.C. § 112, second paragraph.

Applicants respectfully submit that the amendment to the claims has obviated this rejection, which should therefore be withdrawn.

Claims 130-131, 134-136, 143, 146, and 147 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ueda.

Applicants respectfully disagree and request that this rejection be withdrawn for the following reasons.

As set forth in paragraph 6 of Dr. Moses' Declaration ("Moses Declaration" attached hereto as Exhibit I), Ueda does not teach detection of matrix metalloproteinases, as claimed by

the instant invention. Rather, Ueda teaches "detection of cysteine proteinases, an entirely different class of protease enzymes that are distinguishable in structure and function from matrix metalloproteinases." (Moses Declaration ¶ 6.) Therefore, that Ueda does not anticipate the claimed invention.

Claims 130-131, 134, 146, 150, 154-155, 158-160, and 162 were rejected under 35 U.S.C. § 102(b) as being anticipated by Margulies.

Applicants respectfully disagree and request that this rejection be withdrawn for the following reasons.

The present invention is directed to a non-invasive method for facilitating the diagnosis of cancer of an epithelial origin, by obtaining a urine sample from a subject; detecting the presence or absence of a matrix metalloproteinase having molecular weight of at least 50 kDa in the urine sample; wherein a matrix metalloproteinase in the urine sample is indicative of a cancer of an epithelial origin. This method is not taught by Margulies.

Margulies concluded that urinary MMPs were present largely as proteolytic fragments of intact enzymes. Margulies showed no predictive value in detection of MMP-2 or MMP-9 within the cancer cohort, with the exception of a Mr 43,000 MMP-2 **fragment**, which statistical analysis suggested could be used as a potential marker for TCC of the bladder but **not** for renal or prostate carcinoma. See, page 47, column 2, lines 20-23, of the Marguelies paper which states the "...Western blot demonstrated that the major form of the enzyme in the urine was an amino terminal **fragment** with a molecular weight of approximately 45,000 kDa [emphasis added]." Additonally, Figure 4 of the Margulies paper shows that the 45 kDa fragment was more prominent in the TCC pateients compared to the controls (See page 47, column 2, lines 28-31).

Accordingly, Margulies does not teach an association between an MMP of at least 50 k kDa and cancer, as in the claimed methods. Thus, the Margulies reference does not anticipate the claimed invention.

Claims 130-131, 136, and 146 were rejected under 35 U.S.C. § 102(a) as being anticipated by Guolan.

Applicants respectfully disagree and request that the rejections be withdrawn for the following reasons.

As set forth in paragraph 6 of the Moses Declaration, Guolan does not teach detection of matrix metalloproteinases, as claimed by the instant invention. Rather, Guolan teaches "detection of cysteine proteinases, an entirely different class of protease enzymes that are distinguishable in structure and function from matrix metalloproteinases." (Moses Declaration ¶ 6.) Therefore, Guolan does not anticipate the claimed invention and the rejection should be withdrawn.

Claims 130-131, 136, 144, and 146 were rejected under 35 U.S.C. § 102(a) as being anticipated by Okubo.

Applicants respectfully disagree and request that the rejections be withdrawn for the following reasons.

The Examiner alleges that Okubo anticipates the claimed invention for teaching the use of an antibody to the kininogen-calpain complex for the diagnosis of hepatic disease. As stated by Dr. Moses: "[w]hile calpains are members of the protease family, calpains are not metalloproteases, and certainly not *matrix* metalloproteinases." (Moses Declaration ¶ 8.) Accordingly, Okubo does not anticipate the claimed invention because Okubo does not teach detection of matrix metalloproteinases, as claimed by the present invention.

Claims 130-137, 139, 142, 146-148, 160, and 162 were rejected under 35 U.S.C. § 102(a) as being anticipated by Brunner.

Applicants respectfully disagree and request that the rejections be withdrawn for the following reasons.

As set forth in paragraph 9 of the Moses Declaration "[m]atrix metalloproteinases are proteolytic enzymes that degrade extracellular matrix. Brunner discloses that increased concentrations of the inhibitor of the protease or the non-proteolytic matrix-degrading enzyme has been established to be a prognostic factor indicating a poor prognosis for the patient having the type of malignant tumor in question. While Brunner teaches detection of inhibitors of

proteases, the instant invention pertains to detection and correlation of the presence or absence of the matrix metalloproteinase in a sample, thereby facilitating the diagnosis of a matrix metalloproteinase-associated cancer." Thus, Brunner does not anticipate the claimed invention.

Claims 132-133, 138-142, 145, 148-149, 151-153, 156, 157 and 161 were rejected under 35 U.S.C. § 103(a) as being unpatentable over each of Ueda, Margulies, Guolan, and Okubo.

For the reasons set forth above, which are incorporated herein, Applicants respectfully submit that the combination of cited references would not teach or suggest the present invention. Accordingly, the rejection should be withdrawn.

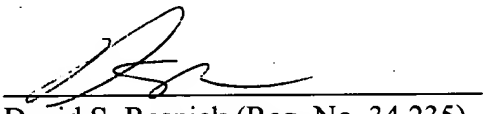
CONCLUSION

In view of the above and foregoing, it is respectfully submitted that the claims now on file are believed to be in condition for allowance, and prompt and favorable action is earnestly solicited. Should there be any question concerning this response or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Authorization is hereby given to the Commissioner to charge any deficient fees or to credit any overpayment to account no. 50-0850.

Date: 1/12/04

Respectfully submitted,



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